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Treatment of Agnogenic Myeloid Metaplasia With Danazol: A Report of Four Cases

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Peripheral cytopenias are common in patients with agnogenic myeloid metaplasia (AMM). They are an important cause of morbidity and mortality, and their treatment is difficult. We report on 4 patients with AMM and severe cytopenia treated with danazol (400–600 mg/day). Three of them became independent of red blood cell (RBC) transfusion, while the other had a slight reduction in RBC requirement. In addition, correction of thrombocytopenia and disappearance of splenomegaly were observed in 1 and 2 patients, respectively. No side effects were observed. In our experience, danazol appears effective and safe in the subset of patients with AMM whose disease is mainly characterized by bone-marrow failure. These data warrant further studies to evaluate this treatment and explore its mechanism of action. © 1996 Wiley-Liss, Inc.

Key words: agnogenic myeloid metaplasia, danazol

INTRODUCTION

Agnogenic myeloid metaplasia (AMM) is a heterogenous disease whose symptoms are related to bone-marrow failure and/or the consequences of an enlarged spleen. No curative therapy is currently available, and the management of patients with severe cytopenias and prominent splenomegaly is difficult. Treatment modalities include transfusional support, cytostatic agents such as hydroxyurea, steroids, α-interferon, and androgens, and in some instances splenectomy, but none of them have been demonstrated to improve survival or to delay the worsening of bone-marrow fibrosis [1,2]. Danazol is a synthetic, attenuated androgen, with reported efficacy on thrombocytopenia of patients with idiopathic thrombopenic purpura (ITP) [3] and in myelodysplastic syndromes (MDS) [4–6]. We report on 4 patients with AMM in whom danazol induced a clear improvement of hematological condition by suppressing or reducing the requirement of red blood cell (RBC) transfusional support.

CASE REPORTS

In each case, the diagnosis of AMM was supported by cytological examination of blood smears, characteristic bone-marrow features with fibrosis, and ^{111}Indium chloride scanning demonstrating hepatosplenic metaplasia. All patients had negative antiglobulin tests, and none of them had a proliferative disease with elevated white blood cell count at time of danazol therapy. The 4 patients received RBC transfusion regularly in order to maintain a hemoglobin level of over 7–8 g/dl. The main hematological parameters before and after treatment with danazol are shown in Table I.

Patient 1 is a 61-year-old man who presented in November 1992 with splenomegaly, anemia, and thrombocytopenia. Treatment with danazol (600 mg/day) and RBC transfusional support were initiated. The transfusional requirement progressively decreased from two RBC packs every 3 weeks at time of diagnosis to two RBC packs every 2 months 18 months later. Since October 1994 he has not required any transfusions, the platelet count has normalized, and the spleen is no more felt. A bone-marrow biopsy performed in November 1995 showed the unchanged persistence of fibrosis.

Patient 2 is a 52-year-old woman who presented in 1988 with moderate spleen enlargement and severe aregenerative anemia. She received RBC packs thrice over a period of 16 months. Since the initiation of danazol (600 mg/day for 3 years, and then 400 mg/day), she has

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TABLE I. Blood Counts in Four Patients Before and After Treatment With Danazol

Patient	Hb (g/dl)		Plt (10^9/l)		Transfusion dependency	Spleen size (cm below costal margin)		Duration of response (months)
	Before	After	Before	After		Before	After	
1	7	12.2	49	237	No	4	0	16+
2	6.1	11	248	372	No	1	0	60+
3	6.8		325	250	Yes[a]	0	0	6+
4	9.7	10.5	50	70	No	8	5	42

[a]RBC requirement decreased from two RBC packs every 2 weeks to two RBC packs every 3 weeks.

not required any further RBC transfusions during the subsequent 5 years. The spleen size is normal, and hemoglobin level is stable at 11 g/dl.

Patient 3 is an 81-year-old woman who presented in 1990 with severe anemia (hemoglobin, 6.8 g/dl) and thrombocytosis (platelet count, 1,000 × 10^9/l). There was no splenomegaly. She required two RBC packs every month during 3 years, and then every other week before danazol (400 mg/day) was introduced in November 1994. After 9 months of treatment, the patient still needs transfusional support, but at longer intervals (two RBC packs every 3 weeks).

Patient 4 is a 64-year-old man in whom AMM was diagnosed in 1990. He presented with anemia (hemoglobin, 5.9 g/dl), severe thrombocytopenia (platelet count, 20 × 10^9/l) with recurrent bleeding manifestations, and enlarged spleen (8 cm below the costal margin). He first received α-interferon for 3 weeks, but this was rapidly discontinued because of the worsening of cytopenias. He was then given prednisolone (1/2 mg/kg) without improvement of RBC requirement (two RBC packs every 2.5 weeks). Five courses of cytarabine and hydroxyurea were administered between December 1990–March 1991, resulting only in a significant decrease of spleen size. In March 1991, danazol treatment (600 mg/day) was begun along with steroids (prednisone 1/2 mg/kg) until September 1991, and then danazol (400 mg/day) was administered alone. From March 1991–September 1994, the patient required only one RBC transfusion. The hematologic condition worsened thereafter, despite continuation of danazol, and the patient finally died from bleeding in December 1995.

DISCUSSION

In these 4 patients with AMM, treatment with danazol significantly improved hematological status, especially by correcting anemia and reducing RBC dependency. Three of them experienced prolonged transfusion independency (16 months+, 42 months, and 60 months+), whereas the remaining patient had only a slight reduction in RBC requirement. In addition, correction of thrombocytopenia and disappearance of splenomegaly were observed in 1 and 2 patients, respectively. However, it is noteworthy that in all cases, symptoms were predominantly related to bone-marrow failure, but not to massive splenomegaly or proliferative features. Among hematological disorders, danazol was first reported to be effective in immune-mediated thrombocytopenia [7] and autoimmune hemolytic anemia (AIHA) [8]. Some reports have also suggested the usefulness of this agent in MDS patients with thrombocytopenia [9]. The mechanism of action of danazol still remains unclear. In the MDS setting, improvement of blood counts does not appear related to the modulation of ineffective haematopoiesis. Most MDS patients have markedly elevated platelet-associated IgG (PA1gG), elevated plasma platelet-bindable IgG (PB1gG), and an increased number of monocyte Fcγ receptors. Treatment with danazol was associated with a decrease of monocyte Fcγ receptors without significant alterations of PA1gG or PB1gG levels, suggesting reduced platelet destruction by abnormal macrophages. Therefore, danazol may indirectly improve cytopenia by decreasing the number of monocyte Fcγ receptors [9]. Such a mechanism has also been suspected in AIHA and ITP [8,10]. Danazol therapy has been reported in only 1 AMM patient, resulting in rapid but transient (only 2 months) improvement of severe cytopenias [11]. In this case, the benefit of danazol could not be explained by an androgenic effect nor by a modulation of the immune system via glucocorticoid receptors, since stanozolol, norethandrolone, and prednisolone had previously failed to improve hematological parameters. In our patients, the time to full-treatment efficiency was longer and the duration of response to danazol therapy much more prolonged than in this single observation. This may be compared to the results obtained with metenolone in the treatment of AMM [12]. No adverse effect was observed. Based on our experience, danazol therapy appears effective and safe in the subset of patients with AMM whose disease is mainly characterized by bone-marrow failure. This provides a basis for larger studies to be initiated for exploration of the mechanism of action of danazol.

REFERENCES

1. Dalla KP, Zeigler ZR, Shadduck RK: α-interferon in myelofibrosis: A case report. Br J Haematol 86:654–656, 1994.

2. Tefferi A, Silverstein MN, Noël P: Agnogenic myeloid metaplasia. Semin Oncol 22:327–333, 1995.
3. Ahn YS, Rocha R, Mylvaganam R, Garcia R: Long-term danazol therapy in autoimmune thrombocytopenia: Unmaintained remission and age dependant response in women. Ann Intern Med 111:723–728, 1989.
4. Avilés A, Rubio ME, Gomez J, Medina ML, Gonzalez-Llaven J: Randomized study of danazol vs. placebo in myelodysplastic syndromes. Arch Invest Med (Mex) 20:183–188, 1989.
5. Catalano L, Selleri C, Montuori N, Fratellanza G, Notaro R, Fontana R, Formisano S, Rotoli B: Danazol for myelodysplastic syndromes. Br J Haematol 85:230–238, 1993.
6. Wattel E, Cambier N, Caulier M, Sautière D, Bauters F, Fenaux P: Androgen therapy in myelodysplastic syndromes with thrombocytopenia: A report on 20 cases. Br J Haematol 87:205–208, 1994.
7. Ahn YS, Harrington WJ, Simon SR, Mylvaganam R, Pall CM, So AG: Danazol for the treatment of idiopathic thrombocytopenia purpura. N Engl J Med 40:1396–1399, 1983.
8. Ahn YS, Harrington WJ, Mylvaganam R, Ayub J, Pall LM: Danazol therapy for autoimmune hemolytic anaemia. Ann Intern Med 102:298–301, 1985.
9. Stadtmauer EA, Cassileth EA, Edelstein M, Abraham J, Schreiber AD, Nowel PC, Cines DB: Danazol treatment of myelodysplastic syndromes. Br J Haematol 77:502–508, 1991.
10. Schreiber AD, Chien P, Tomaski A, Cines DB: Effect of danazol in immune thrombocytopenia purpura. N Engl J Med 316:503–508, 1987.
11. Chabannon C, Pegourie B, Sotto JJ, Hollard D: Clinical and hematological improvement in a patient receiving danazol therapy for myelofibrosis with myeloid metaplasia. Nouv Rev Fr Hematol 32:165–166, 1990.
12. Zittoun R, Bernadou A, Blanc CM, Bilski-Pasquier G, Bousser J: Méténolone dans le traitement des insuffisances médullaires. Presse Med 76:445–448, 1968.